



Psychoactive drug development, authorization, and introduction to the market: The case of methylphenidate

| Review

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Abstract: Following the thalidomide (Softenon) disaster in the 1960s, the registration process for new drugs became more rigorous. Under the stricter regulations, manufacturers of new drugs are required to fulfil many regulations and conduct various studies before a drug can be approved. Methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents was available on the market before the creation of new regulatory authorities. This means that these authorities have not published the balance of efficacy and side effects of methylphenidate. This is an undesirable situation as methylphenidate is an amphetamine, the long-term effects of which are unknown. Although methylphenidate reduces ADHD-related behaviours in the short term, it has not been shown to demonstrate clinically relevant effects in reducing impairment. Independent researchers have not been able to show any long-term efficacy of methylphenidate in children and adolescents. The European Medicines Agency (EMA) rejected the marketing authorisation of methylphenidate for adults in 2010. The drug was approved in Germany; without the conducting of new studies, this drug was approved by the EMA through a mutual recognition procedure. Consequently, methylphenidate is now available in the whole European Union. Cochrane researchers have rejected a systematic review on this drug in adults with ADHD due to the very low quality of the available clinical trials. There is an urgent need for well-conducted long-term trials, free of bias, to assess the harms and benefits of methylphenidate in adult ADHD. In addition, the rules for granting a marketing authorisation of new drugs should ensure that clinical relevance rather than statistically significant effects becomes the most important endpoint of clinical trials investigating the efficacy of drugs.

Keywords: Psychoactive drugs; registration process; marketing authorisation; statistical significance; clinical relevance; methylphenidate; attention deficit hyperactivity disorder; placebo.

1. Introduction

In the European Union (EU), more than 3,000 drugs are approved for use in humans [1]. More than 50% of European citizens use drugs, largely for chronic use, especially psychoactive drugs [2]. The regulatory authority, the European Medicines Agency (EMA), bases its decisions regarding market approval of new drugs on the clinical study reports (CSRs) provided to them by the industry. These very large sets of data sometimes contain

several hundred thousand pages. A decision of the European Ombudsman requires the publication by the EMA of these CSRs on their website. However, the detailed raw data on which claims of efficacy and side effects of these drugs are based are not known. These are considered trade secrets of the manufacturers. This data, however, should be made available to doctors, pharmacists, researchers and patients in order that the drugs may be used with confidence.

This article describes how drugs are studied, authorised and released onto the market. After a brief description of the registration process, an overview is given of the main criteria for establishing efficacy of psychoactive drugs, with special focus on methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD).

2. Introduction of regulatory authorities

In the late 1950s and early 1960s, a medical disaster resulted from the use of the drug thalidomide (Softenon). This drug was developed in West Germany and was marketed in 1957 by the manufacturer Grünenthal as a sleeping agent, painkiller and anti-emetic in pregnancy. It caused very serious abnormalities in children, particularly short or missing arms and legs (phocomelia) and was therefore withdrawn from the market in 1961.

Prior to the thalidomide tragedy, some European and North American countries had introduced more stringent controls on the supervision of (new) medicines. Regulatory authorities were created and given responsibility for the supervision of medicines. In the EU today, the tasks of these national authorities have largely been assumed by the EMA. The United States of America was spared the Softenon disaster by an alert researcher, Frances Kelsey, who, sceptical of the data supplied by the manufacturer on the use of the drug during pregnancy, advised that it should not be admitted to the American market.

It is the responsibility of the regulatory authority to assess the efficacy and side effects of new drugs on the basis of the data supplied (the CSRs) by the manufacturer. If that balance is positive, a marketing authorisation will be issued and the manufacturer may bring the drug to the market for a specified indication and specified patient groups. A manufacturer does not need to include all indications of a drug in the application and may not do so if it does not attach importance to the authorisation for a particular indication. The reason for this may be that the manufacturer suspects that the drug will be prescribed even without registration. This is called off-label prescription. Off-label means that the authorities have not produced a balance of the efficacy and side effects of a drug for a specific therapeutic indication. Off-label prescription is associated with more and serious side effects [3].

3. Requirements for marketing authorisation of new drugs

Manufacturers are required to conduct considerable research in order to be granted a market authorisation. The EMA requires the submission of data on pharmacological characteristics of the drug, including data on (1) pharmacokinetics, i.e. how the drug is absorbed into the bloodstream, to which organs and/or organ systems it is distributed in the body, how it is metabolized and how it is excreted, and on (2) pharmacodynamics, i.e. the mode of action by which the drug exerts its effects in the body. Furthermore, the manufacturer must conduct studies on animals and show whether the drug is safe during pregnancy and breastfeeding.

3.1. Phase I, II, III and IV studies

The manufacturer is required to perform four types of studies in humans: phase I, II, III and IV studies [4]. A phase I study is conducted with a limited number of healthy individuals. The aim is to study how the drug is absorbed and metabolized in the body and how it is excreted from the body, and especially what side effects it causes. In a phase II study, the efficacy of the drug is studied in a limited number of patients (up to some hundreds) with a certain disease. Varying dosages of the drug are administered and the side effects are recorded. Phase III studies are performed in a large group of selected patients, sometimes thousands. The efficacy and side effects of the new drug are compared to a control group who receive placebo or the currently used standard treatment. After phase III trials, manufacturers can apply for a marketing authorisation and if this is granted, they can introduce the drug to the market. After the authorisation phase, phase IV studies or post-marketing surveillance studies are performed. The aim is to learn more about the safety and adverse effects in the general population.

3.2. Statistically significant effects

A major requirement for a manufacturer of a new drug is to show that the drug performs better than placebo. In the statistical analysis, the threshold has been put at the 0.05 level. This level is arbitrary and was set more than a century ago when breed-improvement techniques were developed and researchers had to decide which gain in crops constituted a real improvement. Thus, a statistically significant difference is actually only a mathematical agreement; it does not relate to whether patients feel better or their condition improves. In

practice, drugs are given a marketing authorisation when it has been shown that the drug works better than placebo.

3.3. Endpoints

The efficacy of drugs does not have to be shown in regard to hard clinical endpoints such as mortality and morbidity. For instance, hypertension is a risk factor for myocardial infarction, stroke and premature death. A blood pressure lowering drug may be registered when it can be shown to reduce blood pressure more effectively than placebo to a statistically significant degree. There is no need to show that it prevents myocardial infarction or death. Blood pressure, then, is a so-called surrogate endpoint.

4. Marketing authorisation of psychoactive drugs

For drugs used in psychiatry there are no hard clinical endpoints and no surrogate endpoints. Diagnoses are made on the basis of questionnaires and are subjective; there are no laboratory tests or imaging techniques that assist in diagnosing a psychiatric disorder.

Before turning to ADHD drugs, two groups of drugs used in psychiatry will be discussed to illustrate what was proven in regard to their efficacy when they were released onto the market.

4.1. Antidepressant drugs

It is assumed that antidepressants show a statistically significant improvement compared to placebo in the treatment of depression. But a statistically significant effect does not mean that the patient improves or feels better. As an example: in a hypothetical study, patients with major depressive disorder have a mean Hamilton Depression Rating Scale (HAM-D) score [5] of 20. One group of patients receives an antidepressant and after 6 to 8 weeks (the mean duration of a trial) the HAM-D-score will be reduced to 12. The other group receives placebo and their HAM-D-score will drop to 13 after 6 to 8 weeks. The difference between the two groups is one point on the HAM-D, and when the groups are large enough (e.g. a few hundred participants), this difference is statistically significant. But there is no doctor or patient who can observe or perceive such a difference.

A far more helpful endpoint is the clinical relevance of the effect. Clinical relevance relates to whether a certain treatment really helps patients. The minimum score for a clinically relevant difference is 3 on the HAM-D [6], but critical researchers have argued that it should actually be 7 or 8 [7]. The regulatory authorities do not

require that manufacturers prove their drug has clinically relevant effects. If the authorities demanded clinically relevant effects of antidepressants, probably no antidepressant would have gained a marketing authorisation.

4.2. Antipsychotic drugs

In psychosis and schizophrenia, positive and negative symptoms are distinguished. A commonly used instrument to measure and monitor the severity of symptoms in research is the Positive and Negative Syndrome Scale (PANSS) [8]. This is a list of 30 questions, with a maximum score of 210 points. In most studies, patients have an average of 91 points. Stefan Leucht and fellow researchers from the Technical University of Munich have, by merging a number of assessment scales, calculated that an improvement of at least 15 points on the PANSS scale is a clinically relevant improvement in the patient [9]. The placebo studies with antipsychotic drugs presented to the US Food and Drug Administration (FDA) in the years between 1991 and 2009 show that the improvement was only 6 points, and since that is statistically significant, these drugs were granted a marketing authorisation [10]. This reaffirms that psychoactive drugs are not registered because patients feel better, but because manufacturers have demonstrated a mathematical difference to placebo.

5. Methylphenidate for ADHD

Methylphenidate and atomoxetine are drugs registered for the treatment of ADHD. Clonidine is used off-label. Dexamphetamine is also used but is not registered as a drug. Methylphenidate and dexamphetamine both belong to the amphetamine group of drugs. Amphetamines have been used in the United States for many decades to treat symptoms of hyperactivity and attention deficit. Amphetamines were also used by soldiers in the Second World War [11], enabling them to perform for longer, with less need for sleep. Methylphenidate in the Netherlands is covered by the so-called Opium law. The drug is also regarded as dope in sports and cannot be exported beyond the Schengen countries without a doctor's certificate.

The first drug that was approved for the treatment of symptoms of hyperactivity or lack of attention was methylphenidate. It was internationally available since 1954 and received a marketing authorisation in the early 1960s before more stringent rules for the registration process were introduced following the Softenon disaster. Therefore, no actual balance of efficacy and side effects

has been published by the authorities. This drug is now used for the treatment of hyperactivity in children, and since 2017 also in adults.

5.1. Therapeutic indication in children and adolescents

Methylphenidate has a marketing authorisation in the EU as part of an extensive treatment program for ADHD in children of six years and older, in which ortho-pedagogic treatment only is found to be insufficient [12]. The treatment must take place under the supervision of a specialist in the field of behavioural disorders in children. The diagnosis must be made in accordance with the criteria of the DSM-IV (or DSM-5) or the guidelines of the International Classification of Diseases (ICD-10) and should be based on a full disease history and patient evaluation [13,14]. The diagnosis cannot be made solely on the basis of the presence of one or more behavioural characteristics [12]. Of particular importance is that treatment with methylphenidate is not indicated in all children with ADHD. The decision to use the drug must be based on a thorough assessment of the severity and chronicity of the child's behaviours in relation to age [12].

5.2. Mode of action

Methylphenidate has a sympathomimetic effect and a stimulating effect on the central nervous system. Sympathomimetic effects are, for example, an increase in blood pressure and heart rate. Furthermore, methylphenidate acts in the same way and place in the brain as, for example, the hard drugs cocaine, dexamphetamine and 3,4-methylenedioxymethamphetamine (ecstasy) [15].

The administration of amphetamines in hyperactive children seems contradictory. It is assumed that it works by stimulating inhibitory mechanisms. Thus, it is believed that these drugs produce increased attention, clear thinking ability, reduced feeling of fatigue and slight euphoria [16]. How can a drug that is regarded as a stimulant reduce symptoms of hyperactivity and attention deficit? In the product information of methylphenidate, it is stated that the mode of action is not known. However, in certain publications it is claimed that amphetamines are, in fact, dopamine-reuptake inhibitors [17]. Comparable to serotonin-reuptake inhibitors, amphetamines increase the dopamine content in the synapses in the brain.

Chronic use of amphetamines can lead to psychological and physical dependence [16] and may give rise to adverse reactions, such as hallucinations,

delusions, stereotypical behaviours, movement disorders and the onset of psychosis [18].

5.3. Efficacy and side effects

The published meta-analyses on the efficacy of amphetamines and other substances in the treatment of ADHD in children and adolescents show that, in the short term, the drugs reduce ADHD-related behaviours as compared to placebo to a statistically significant extent [19–21]. As with other psychiatric disorders, there is a significant placebo effect, sometimes up to more than 30%. Yet, in all these studies methylphenidate was not used according to the registered therapeutic indication because no ortho-pedagogic treatment was offered to the patients before the commencement of the drug. Most studies were short-term, not double-blind and did not measure the most important issue for the user, the impairment. The only long-term study, the Multimodal Treatment study of children with ADHD (MTA), did not show, even after 16 years' follow-up, any differences regarding school results, delinquency or addiction between treatment groups [22].

Major side effects include psychiatric disorders, cardiovascular diseases, growth retardation and reproduction impairments.

5.4. Registration process for adults

Janssen-Cilag, the manufacturer of one form of methylphenidate (Concerta®), submitted an application to the EMA in 2010 for the registration of its drug for the treatment of ADHD in adults [23]. By means of a decentralized procedure, the UK regulatory authority Medicines and Healthcare Products Regulatory Agency (MHRA) rejected this application because the research submitted did not clearly demonstrate the efficacy of methylphenidate, and the safety of the product was not sufficiently guaranteed [24,25]. The safety concerns were largely in relation to cardiovascular and psychiatric side effects, as well as the risk of anxiety, aggression and dependence. A further concern was the potential for abuse, since adults could simulate the disorder. The regulatory authorities have not made these negative conclusions public because they are regarded as trade secrets. They have received hardly any attention in medicine and science or in national and international media.

This situation is quite unique. European psychiatrists prescribe methylphenidate off-label for the treatment of ADHD in adults while the regulatory authorities regard both the efficacy and the side effects of the drug as

negative and, consequently, did not give a marketing authorisation for adults. Remarkably, while methylphenidate may not be prescribed for adults, it is considered efficacious and safe for use in children and adolescents. Despite the fact that the regulatory authority has not issued a marketing authorisation for methylphenidate for the treatment of ADHD in adults, European psychiatrists, in a directive on ADHD, have recommended adult drug treatment with methylphenidate as the first treatment option [26].

5.5. Placebo or nocebo

The starting point in medicine is that no harm is inflicted on the patient: *primum non nocere*. It appears that psychiatrists make an exception to this. They administer drugs to patients with ADHD off-label while the efficacy and safety of the drug is in serious question. We can only hope that such doctors have at least applied a comprehensive informed-consent procedure to adult patients, apprised them of the risks and recorded this in the medical file.

The balance of efficacy and side effects of methylphenidate for the indication ADHD in adults is, in the judgement of the regulatory authority, negative. In other words, the side-effects outweigh the drug's efficacy. Such a drug is not a placebo but a nocebo.

5.6. Mutual recognition

In 2017, Janssen-Cilag made a further attempt to acquire a license in the EU for methylphenidate in the treatment of adults with ADHD. The EMA used the so-called mutual recognition procedure. This is an older procedure, according to which a drug that is licensed in one European country can be licensed in all European countries. The country that granted methylphenidate a license was Germany [27]. Remarkably, the manufacturers did not perform more clinical studies to support their claim for a license. In 2017, the EMA granted marketing authorisation for adults. This decision is puzzling.

5.7. Cochrane review

The Cochrane Collaboration, which is regarded as producing the best available evidence in the diagnosis and treatment in medicine, produced a systematic review and meta-analysis of methylphenidate for adults with ADHD in 2014 [28]. Researchers from the Nordic Cochrane Centre evaluated this review in 2017. They found a number of methodological shortcomings, which are presented in Table 1. These findings led the Nordic

Cochrane Centre to withdraw the systematic review from the Cochrane Library [29]. This unusual measure was necessitated by the very low quality of the trials. The authors concluded that there is an urgent need for well-conducted long-term trials, free of bias, to assess the harms and benefits of central stimulant therapy in adult ADHD.

Table 1. Methodological shortcomings of a Cochrane review on methylphenidate for adults with ADHD [28]

- Cross-over designs compared with parallel-group designs
 - Exclusion of participants with psychiatric comorbidity
 - Absence of functional outcomes and use of clinical outcomes with limited relevance
 - Short trial duration and small trial populations
 - Broken blinding caused by easily recognisable side effects
 - Combining outcome assessments by trial investigators and participants
 - Outcome reporting bias
 - Poor evaluation of cardiovascular and psychiatric harms
 - Conflicts of interest of trialists and systematic reviewers
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6. Discussion

The registration procedures for new drugs became more stringent in the early 1960s following the Softenon tragedy. Producers of new drugs are required, under the new rules, to fulfil many regulations and conduct several studies before a drug can be approved. For psychoactive drugs, statistically significant effects are the mainstay for their approval as there are no hard endpoints and even no surrogate endpoints. However, statistically significant effects do not imply an improvement in the patients' condition or that patients feel better. In other words, the manufacturer does not have to prove that its drug has a clinically relevant effect.

Methylphenidate for the treatment of ADHD in children and adolescents was available on the market before the installation of the regulatory authorities and, thus, the authorities have not published the balance of efficacy and side effects of this drug. This is of concern as

methylphenidate is an amphetamine and its long-term effects are not well studied. Although methylphenidate reduces ADHD-related behaviours in the short term, it has not been shown to demonstrate clinically relevant effects in reducing impairment. Independent researchers have not been able to show any long-term efficacy of methylphenidate in children and adolescents.

The EMA rejected the marketing authorisation of methylphenidate for adults in 2010. Nevertheless, the drug was approved in Germany in 2011. In the absence of new studies, this drug was approved by the EMA in 2017 through a mutual recognition procedure. Consequently, methylphenidate is now available in the entire EU. Cochrane researchers have rejected a systematic review on this drug in adults with ADHD and have withdrawn it from their library.

As the balance of efficacy and safety is negative, methylphenidate for the treatment of ADHD-related behaviours should be regarded as a nocebo. Finally, the rules for granting a marketing authorisation of new drugs should be tightened so that clinical relevance becomes the most important endpoint and not statistically significant effects.

Conflict of interest

The author declares no conflict of interest.

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